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(54) MICRO-CRYSTALLINE COLLAGEN-CONTAINING PHARMACEUTICAL COMPOSITIONS USEFUL FOR TOPICAL APPLICATIONS

(71) We, AVICON, INC. of Fort Worth, in the State of Texas, United States of America, a corporation organized and existing under and by virtue of the laws of the State of Delaware, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to aqueous pharmaceutical compositions containing a pharmacologically active ophthalmic agent.

It is an object of the present invention to provide an improved pharmaceutical composition for topical application to the eye.

According to the present invention, there is provided an aqueous pharmaceutical composition for topical application to the eye, comprising a pharmacologically active ophthalmic agent and 0.1% to 5.0%, by weight, of microcrystalline collagen, based on said composition.

The microcrystalline collagen may, for example, be incorporated in an amount in the range from 0.1 to 0.2% by weight.

Any pharmacologically active ophthalmic agent may be used, the composition of the invention having improved properties (by enhancing the drug action and/or prolonging the duration of the drug action) when applied topically to the eye as compared to the use of the pharmacologically active ophthalmic agent alone.

Preferably, the said pharmacologically active ophthalmic agent is selected from carbachol, a pilocarpine salt, an epinephrine salt, dexamethasone, phenylbutazone, sulphacetamide, hydrocortisone, chlorobutanol, prednisolone acetate, phenylephrine hydrochloride, tropicamide, zinc sulphate, polymixin B sulphate, neomycin sulphate, atropine sulphate, triamcinolone acetonide and mixtures thereof.

Microcrystalline collagen is a collagen material commercially available under the trade name Avitene, manufactured by FMC Corporation, Princeton, New Jersey, U.S.A.

The preparation and properties of microcrystalline collagen are disclosed in British Patents Nos. 1,156,361, 1,224,925 and 1,144,552. As disclosed therein and as used herein, microcrystalline collagen is a new form of collagen in a physical state intermediate between that of swollen collagen fibrils and tropocollagen units. It is water-insoluble, particulate and colloidal, is substantially free of molecular tropocollagen and water-soluble degradation products. The microcrystals or particles consist of bundles of aggregated tropocollagen units and vary in length from that of an individual tropocollagen unit (about 25 to 50 Å) to under 1 micron and have diameters from about 25 Å to some hundreds of Angstrom Units. Desirably, particularly in the practices of this invention, this physical form of collagen should contain at least about 1% by weight of submicron colloidal collagen particles, that is, particles whose maximum dimension in any one direction less than 1 micron. This form of collagen, which is in fact, a water-insoluble, ionizable salt of collagen, is unique in its characteristics of forming an aqueous soliquoid or non-elastic type gel in concentrations of 0.5% dispersed salt, the gel exhibiting a pH of about 3.2±0.5 and having a substantially stable viscosity for at least 100 hours at 5°C. when stored in a closed container. This is in sharp contrast to the aqueous elastic or emulsoid type gels formed by tropocollagen and degraded forms

of collagen, such as gelatin, which thicken or exhibit substantial increases in viscosity on standing to produce rubbery mixes.

As disclosed in the aforementioned patents, this new physical form of collagen is prepared from undenatured collagen by treatment of undenatured collagen with dilute acid solutions having a pH of from 1.6 to 2.7, conveniently between 1.7 and 2.6. The treated collagen is subsequently mechanically disintegrated in an aqueous liquid until at least 1%, preferably 25% to 85% or more, has been reduced to a submicron colloidal size. Collagen fibrils exhibit a morphological repetitive band structure which is destroyed in the preparation of this new physical form of collagen and the individual or microcrystalline particles are fragments of the bands, viz. aggregated tropocollagen units.

The action of the acid is three-fold. First, the acid serves to cause a limited swelling of the fibrils. Second, there is a limited hydrolysis of selective peptide linkages within the noncrystalline or amorphous regions of the collagen fibrils so that subsequent mechanical disintegration permits a ready fragmentation of the weakened morphological bands into microcrystalline particles having dimensions between these of tropocollagen and collagen fibrils. Third, a portion of the acid reacts with free primary amino groups of the collagen to form what may be determined a collagen salt which becomes ionized in the presence of water.

Acids which are satisfactory in the preparation of the microcrystalline collagen employed in the practices of this invention include both inorganic and ionizable organic acids, such as hydrochloric acid, sulphuric acid, hydrobromic acid, phosphoric acid, acetic acid, cyanoacetic acid and citric acid. Phosphoric acid, acetic acid and citric acid are preferred. In lieu of acid, acid salts may be used satisfactorily. Thus, for example, dihydrogen sodium or ammonium phosphates may be substituted for phosphoric acid and ammonium or sodium hydrogen sulphates may be substituted for sulphuric acid.

In the preparation of the collagen employed in the practices of this invention purified bovine hide is the preferred source of collagen. A microcrystalline collagen found to be effective in the practices of this invention comprises a water-insoluble, ionizable partial salt of colagen having a bound ionizable acid content of from 50% to 90% of the theoretical stoichiometric bound acid content, being essentially free of tropocollagen and degraded derivatives thereof and being further characterized in that, when colloidally dispersed in water to form a 0.5% by weight gel wherein at least 10% by weight of the partial salt has a particle size under 1 micron, the gel exhibits a pH of about 3.2 ± 0.5 and exhibits an essentially constant viscosity after 1 hour for at least 100 hours when stored in a closed container at 5°C. with refrigeration Such material is produced by distributing through a body of undenatured fibrous natural collagen an aqueous solution of an ionizable acid having a pH in the range from 1.6 to 2.7, based upon 1% solids concentration, thereupon allowing the acid to react with the available amino groups of the collagen to form a water-insoluble ionizable partial salt of collagen containing 50% to 90% of the theoretical stoichiometric bound acid content while maintaining the temperature below 30°C., and recovering the partial salt essentially free of tropocollagen and degraded derivatives thereof.

The aqueous pharmaceutical compositions comprising the microcrystalline collagen in the form of an aqueous dispersion in accordance with this invention may include any one or more of a number of pharmacologically active ophthalmic agents. By way of example, the following pharmacologically active materials are useful for incorporation in aqueous pharmaceutical compositions containing microcrystalline collagen in accordance with this invention:

chloramphenicol
carbomycin
erythromycin
dihydrostreptomycin
neomycin
aureomycin
terramycin
bacitracin
penicillin
ampicillin
tetracaine
proparacaine
benoxinate
cocaine
procaine
lidocaine
epinephrine
isoniazid
nitrofurans
sulphonamides, such as
sulphanilamide
sulphapyridine
sulphadiazine
sulphathiazole
sulphacetamide
phenylephrine
ephedrine
gentian violet
acriflavine
silver nitrate
quaternary ammonium germicides
atropine
homatropine
scopolamine
cyclopentolate
tropicamide
oxyphenonium
acetylcholine
carbachol
pilocarpine
demercarium
dihydroergocornine
tolazoline
tetraethylammonium chloride
hexamethonium
norepinephrine
physostigmine (eserine)
cortisone
hydrocortisone
prednisolone
dexamethasone
triamicinolone
methylprednisolone
argyrol
phenylmercuric nitrate
chlorazene
mercurochrome
iodine

A more complete listing or identification of pharmaceutical agents useful for incorpora-

of collagen, such as gelatin, which thicken or exhibit substantial increases in viscosity on standing to produce rubbery mixes.

As disclosed in the aforementioned patents, this new physical form of collagen is prepared from undenatured collagen by treatment of undenatured collagen with dilute acid solutions having a pH of from 1.6 to 2.7, conveniently between 1.7 and 2.6. The treated collagen is subsequently mechanically disintegrated in an aqueous liquid until at least 1%, preferably 25% to 85% or more, has been reduced to a submicron colloidal size. Collagen fibrils exhibit a morphological repetitive band structure which is destroyed in the preparation of this new physical form of collagen and the individual or microcrystalline particles are fragments of the bands, viz. aggregated tropocollagen units.

The action of the acid is three-fold. First, the acid serves to cause a limited swelling of the fibrils. Second, there is a limited hydrolysis of selective peptide linkages within the noncrystalline or amorphous regions of the collagen fibrils so that subsequent mechanical disintegration permits a ready fragmentation of the weakened morphological bands into microcrystalline particles having dimensions between these of tropocollagen and collagen fibrils. Third, a portion of the acid reacts with free primary amino groups of the collagen to form what may be determined a collagen salt which becomes ionized in the presence of water.

Acids which are satisfactory in the preparation of the microcrystalline collagen employed in the practices of this invention include both inorganic and ionizable organic acids, such as hydrochloric acid, sulphuric acid, hydrobromic acid, phosphoric acid, acetic acid, cyanoacetic acid and citric acid. Phosphoric acid, acetic acid and citric acid are preferred. In lieu of acid, acid salts may be used satisfactorily. Thus, for example, dihydrogen sodium or ammonium phosphates may be substituted for phosphoric acid and ammonium or sodium hydrogen sulphates may be substituted for sulphuric acid.

In the preparation of the collagen employed in the practices of this invention purified bovine hide is the preferred source of collagen. A microcrystalline collagen found to be effective in the practices of this invention comprises a water-insoluble, ionizable partial salt of colagen having a bound ionizable acid content of from 50% to 90% of the theoretical stoichiometric bound acid content, being essentially free of tropocollagen and degraded derivatives thereof and being further characterized in that, when colloidally dispersed in water to form a 0.5% by weight gel wherein at least 10% by weight of the partial salt has a particle size under 1 micron, the gel exhibits a pH of about 3.2 ± 0.5 and exhibits an essentially constant viscosity after 1 hour for at least 100 hours when stored in a closed container at 5°C. with refrigeration Such material is produced by distributing through a body of undenatured fibrous natural collagen an aqueous solution of an ionizable acid having a pH in the range from 1.6 to 2.7, based upon 1% solids concentration, thereupon allowing the acid to react with the available amino groups of the collagen to form a water-insoluble ionizable partial salt of collagen containing 50% to 90% of the theoretical stoichiometric bound acid content while maintaining the temperature below 30°C., and recovering the partial salt essentially free of tropocollagen and degraded derivatives thereof.

The aqueous pharmaceutical compositions comprising the microcrystalline collagen in the form of an aqueous dispersion in accordance with this invention may include any one or more of a number of pharmacologically active ophthalmic agents. By way of example, the following pharmacologically active materials are useful for incorporation in aqueous pharmaceutical compositions containing microcrystalline collagen in accordance with this invention:

chloramphenicol
carbomycin
erythromycin
dihydrostreptomycin
neomycin
aureomycin
terramycin
bacitracin
penicillin
ampicillin
tetracaine
proparacaine
benoxinate
cocaine
procaine
lidocaine
epinephrine
isoniazid
nitrofurans
sulphonamides, such as
sulphanilamide
sulphapyridine
sulphadiazine
sulphathiazole
sulphacetamide
phenylephrine
ephedrine
gentian violet
acriflavine
silver nitrate
quaternary ammonium germicides
atropine
homatropine
scopolamine
cyclopentolate
tropicamide
oxyphenonium
acetylcholine
carbachol
pilocarpine
demercarium
dihydroergocornine
tolazoline
tetraethylammonium chloride
hexamethonium
norepinephrine
physostigmine (eserine)
cortisone
hydrocortisone
prednisolone
dexamethasone
triamicinolone
methylprednisolone
argyrol
phenylmercuric nitrate
chlorazene
mercurochrome
iodine

A more complete listing or identification of pharmaceutical agents useful for incorpora-

tion in aqueous pharmaceutical compositions containing microcrystalline collagen in the form of aqueous gel in accordance with this invention is to be found in Ocular Pharmacology by William H. Havener, published by The C. V. Mosby Co., St. Louis, Mo., U.S.A. (1966).

The following is a listing of pharmaceutical compositions prepared in accordance with the practices of this invention or which embody the practices of this invention, all the percentages being by weight.

Formulation No.		
1.	Carbachol	0.003—1.0%
	HCl 0.01 N qs pH 3.5	
	Microcrystalline collagen	0.5%*
	Purified (deionized or distilled) water	qs (i.e. sufficient to bring the total to 100%)
2.	Carbachol	0.003—1.0%
	HCl 0.01 N qs pH 3.5	
	Benzalkonium chloride	0.005%
	Microcrystalline collagen	0.5%*
	Purified water	qs
3.	Pilocarpine Hydrochloride	0.32% to 0.01%
	Microcrystalline Collagen	0.5%*
	Purified water	qs
4.	Epinephrine bitartrate	0.05% up to 1.0%
	HCl 0.1 N qs pH 3.8 if required	
	Microcrystalline collagen	0.5%*
	Purified water	qs
5.	Dexamethasone	0.001% up to 0.1%
	Microcrystalline collagen	0.5%*
	Purified water	qs
6.	Dexamethasone acetate	0.001% up to 0.1%
	Microcrystalline collagen	0.5%
	Purified water	qs
7.	Phenylbutazone	0.125% up to 1.0%
	Microcrystalline collagen	0.5%*
	Purified water	qs
8.	Carbachol	0.75%—3.0%
	Benzalkonium chloride	0.005%
	Boric acid	(adj. to pH 3.8)
	Sodium chloride	0.20%
	Microcrystalline collagen	0.5%*
	Purified water	qs
9.	Pilocarpine HCl	0.25%—10%
	Benzalkonium chloride	0.004%
	Phenylmercuric nitrate	0.00133%
	Boric acid	(adj. to pH 3.8)
	Microcrystalline collagen	0.5%*
	Purified water	qs
10.	Sulfacetamide	15%
	Chlorobutanol	0.15%
	Sodium thiosulphate	0.3%
	HCl (1N) to adj. pH	3.8
	Microcrystalline collagen	0.5%*
	Purified water	qs
11.	Sulphacetamide	10.0%
	Prednisolone	0.25%
	Chlorobutanol	0.15%
	Sodium thiosulphate	0.1%
	Citrate buffer	
	HCl (1N) to adjust pH 3.9	
	Microcrystalline collagen	0.5%*
	Purified water	qs
12.	Hydrocortisone	0.5%
	Phenylephrine hydrochloride	0.12%
	Benzalkonium chloride	0.004%

Phenylmercuric nitrate	0.00133%
Sodium bisulphite	0.1%
Boric acid	1.50%
Polysorbate (sold under the Registered Trade Mark "Tween") 80	0.4%
Microcrystalline collagen	0.5%*
Purified water	qs
13. Phenylephrine hydrochloride	0.12%
Chlorobutanol	0.15%
Citrate buffer (adj. to pH 3.8)	
Microcrystalline collagen	0.5%*
Purified water	qs
14. Hydrocortisone	0.5%, 2.5%
Benzalkonium chloride	0.004%
Phenylmercuric nitrate	0.00133%
Boric acid	1.5%
Surfactant, e.g. polysorbate ("Tween") 80	0.4%
Microcrystalline collagen	0.5%*
Purified water	qs
15. Benzalkonium chloride	0.002%
Chlorobutanol	0.15%
Microcrystalline collagen	0.5%*
Purified water	qs
16. Tropicamide	0.5%, 1.0%
Phenylmercuric nitrate	0.002%
Sodium nitrate	1.18%
Nitric acid (titrate to adjust pH 3.8)	
Microcrystalline collagen	0.5%*
Purified water	qs
17. Zinc Sulphate	0.25%
Benzalkonium chloride	0.01%
Citrate buffer (adj. pH to 3.8)	
Microcrystalline collagen	0.5%*
Purified water	qs
18. Polymixin B sulphate	16,250 units/ml
Neomycin sulphate	3.5 mg base/ml
Phenylephrine HCl	0.12%
Boric acid (qs adj. pH 3.8)	
Sodium chloride	0.2%
Microcrystalline collagen	0.5%*
Purified water	qs
19. Polymixin B sulphate	16,250 units/ml
Hydrocortisone acetate	0.5%, 1.5%
Benzalkonium chloride	0.004%
Neomycin sulphate	3.5 mg base/ml
Citrate or Acetate buffer (pH adj. to 3.8)	
Sodium chloride	0.2%
Microcrystalline collagen	0.5%*
Purified water	qs
20. Atropine sulfate	1.0%
Prednisolone	0.25%
Chlorobutanol	0.15%
Boric acid (qs adj. pH to 3.8)	
Microcrystalline collagen	0.5%*
Purified water	qs
21. Dexamethasone	0.1%
Benzalkonium chloride	0.004%
Phenylmercuric nitrate	0.00133%
Sodium chloride	0.5%
Surfactant, e.g. Polysorbate ("Tween") 80	0.05%
Citrate or Acetate Buffer (pH adj. to 3.8)	
Microcrystalline collagen	0.5%*

	Purified water	qs
22.	Triamcinolone acetonide	0.1%
	Benzalkonium chloride	0.004%
	Phenylmercuric nitrate	0.00133%
	Mineral oil	1%
	Isopropyl myristate	2%
	1-Hexadecanol	8%
	Lanolin	1%
	Sodium dodecylsulphate	1%
	Sorbitol hydrate	3%
	Glycerine	3%
	Triethanolamine	1%
	Lauric acid	6%
	Microcrystalline collagen gel solids qs (may be varied)	1.33%
23.	Triamcinolone acetonide	0.1%
	Benzalkonium chloride	0.004%
	Phenylmercuric nitrate	0.00133%
	Ethoxylan 100	1.0%
	Propylene glycol	3.5%
	Surfactant, e.g. Tween 80	2.5%
	Microcrystalline collagen gel solids	qs
24.	Triamcinolone acetonide	0.1%
	Benzalkonium chloride	0.004%
	Phenylmercuric nitrate	0.00133%
	Isopropanol	30%
	Microcrystalline collagen	1.0%
	Purified water	qs

*The concentration of microcrystalline collagen may be varied, for example, from 0.1 to 5.0% by weight.

Tests were carried out to demonstrate the enhancement of pharmacological activity in compositions containing microcrystalline collagen over other similar compositions in the absence of microcrystalline collagen but including other agents, such as hydroxypropylmethyl cellulose (HPMC) conventionally employed in pharmaceutical compositions, particularly pharmaceutical compositions containing a pharmacologically active ophthalmic agent and useful for topical application to the eye. For example, the following formulations made up of an aqueous disperseion of microcrystaline colagen and containing various pharmacologically active agents were found to exhibit improved biological activity:

Formulation A	
Carbachol	0.1%
HCl 0.01 N qs pH 3.5	
Microcrystalline collagen	0.5%
Purified water	qs

Formulation B	
Carbachol	0.1%
HCl 0.01 N qs pH 3.5	
Benzalkonium chloride	0.005%
Microcrystalline collagen	0.5%
Purified water	qs

The presence of microcrystalline collagen in the form of an aqueous dispersion in such formulations enhanced the drug action and/or prolonged the duration of the drug action and, therefore, microcrystalline collagen is a useful component of the vehicle or carrier for the pharmacologically active agent.

Although emphasis has been placed in the description of this invention as being directed to liquiform aqueous pharmaceutical compositions containing microcrystalline collagen, the compositions embodying the practices of this invention might also be salve or semi-solid or gel-like compositions or solid-gel-like compositions.

The following examples are illustrative of the practices of this invention and the benefits obtainable therefrom.

Example No. 1

Formulation Nos. 1 and 2—Carbachol 0.1%
Test animal: Albino rabbits
Biological end point observed: pupil size *vs* time
n=6; Dosed by syringe, topically

Treatment Formulation	%	Mean pupil Size in Rabbits Minutes 0	10	20	30	Hours 1.5	2.5	3.5	4.5	5.5
Carbachol in Saline with B.C. 1:20,000	0.1	4.2	3.1	2.9	2.8	2.8	3.0	3.5	3.4	3.7
Carbachol in HPMC 1.0% with B.C. 1:20,000	0.1	4.2	3.2	2.9	2.8	3.1	3.4	3.7	3.8	4.1
Carbachol in microcrystalline Collagen (Formulation No. 1)	0.1	4.3	2.1	1.8*	1.9*	2.1*	2.5	2.8	3.1	3.4
Carbachol in microcrystalline collagen (Formulation No. 2)	0.1	4.2	2.1	1.7*	1.7*	1.8*	2.0	2.8	2.9	3.2

*enhanced pharmacologic effect; B.C.=benzalkonium chloride

Formulation No. 3; Pilocarpine Hydrochloride
Test animal: Albino rabbits
Biological end point observed: Pupil size (onset and duration)
n=6 Dosed by syringe, topically

Treatment Formulation	Mean Area Under Response Curve $(CM)^2$ Drug Concentration 0.32	0.1	0.032	0.01
Pilocarpine HCl in Saline	73.7	73.1	57.0	19.2
Pilocarpine HCl in HPMC 1.0%	75.5	71.3	63.8	20.1
Carbachol in Microcrystalline collagen (Formulation No. 3)	101.0*	7.4.3	47.6	21.0

*enhanced pharmacologic effect.

Formulation No. 4: Epinephrine bitartrate
Formalin Induced Ocular Hypertension Model (Proc. Soc. Exp. Biol. & Med. 131: 637—641, 1969)
Test animal: Albino rabbits
Biological end point observed: Intraocular pressure
n=4 Dosed by syringe, topically

Treatment Formulation	Intraocular Pressure mm Hg Drug Concentration 2%	1%	0.5%	0.25%	0.125%	0.623%
Epinephrine bitartrate in saline	18.5	20.4	24.6	—	—	—
Epinephrine bitartrate in microcrystalline collagen (Formulation No. 4)	—	18.8*	16.8*	22.3	20.9	24.8

*enhanced pharmacologic effect.

Calculated potency ratio shows test formulation (No. 4 to be 5.13 times as potent as the drug in saline

Water Loading Induced Ocular Hypertension Model
Test animal: Albino rabbits
Biological end point observed: Intraocular pressure
n=4 Dosed by syringe, topically

Treatment Formulation	Intraocular pressure mm Hg Drug Concentration 2%	1%	0.5%	0.25%	0.125%
Epinephrine bitartrate in saline	20.0	22.3	23.4	—	—
Epinephrine bitartrate in microcrystalline collagen (Formulation No. 4)	—	—	17.9*	18.9*	22.7*

*enhanced pharmacologic effect.

Calculated potency ratio shows test formulation (No. 4) to be 4.16 times as potent as the drug in saline

Formulation No. 5: Dexamethasone alcohol

Formulation No. 6: Dexamethasone acetate
Immuno-uveitis Test for Anti-inflammatory agents (Proc. Scc. Exp. Biol. and Med. April, 1970)
Test Animal: Albino rabbits
Biological end point observed: Ocular inflammation (as *S* control)
n=6 or 12 Dosed by syringe, topically

Treatment Formulation	Ocular Inflammation (% Control) Drug Concentration 0.1%	0.032%	0.01%	0.0032%
Dex. alcohol in HPMC 0.5%	51.9	66.0	83.3	—
Dex. alcohol in microcrystalline collagen (Formulation No. 5)	59.5	70.3	56.8*	86.6*
Dex. acetate in HPMC 0.5%	60.0	62.5	76.1	82.7
Dex. acetate in microcrystalline collagen (Formulation No. 6)	67.6	59.5	75.6	83.9

*enhanced pharmacologic effect.

Croton Oil Induced Ear Edema Assay: A Topical Dermatological Anti-inflammatory Assay (Endocrinology 77: 625—634, 1965)
Test animal: Albino rats
Biological end point observed: Edema of ear (1% of control
n=6 Drug applied topically

Treatment Formulation	% Decrease from Control in Ear Edema Drug Concentration in mg 0.1 mg	0.01 mg	0.001 mg
Dex. alcohol in Ointment Base #4	44.8%	25.0%	10.0%
Dex. alcohol in Microcrystalline collagen (Formulation No. 5)	46.6%	34.6%*	21.0%*
Dex. acetate in Ointment Base #4	41.2%	28.0%	14.2%
Dex. acetate in Microcrystalline collagen (Formulation No. 6)	55.5%	38.0%*	22.1%*

*enhanced pharmacologic effect.
Base #4=A refined grade of While Petrolatum, U.S.P. (Pennsylvania Refining Co., Butler, Pa.)
Dex. acetate—Calculated potency ratio shows test formulation (No. 6) to be 4.7 times as potent as the drug in ointment Base #4.

WHAT WE CLAIM IS:—

1. An aqueous pharmaceutical composition for topical application to the eye, comprising a pharmacologically active ophthalmic agent and 0.1% to 5.0%, by weight, of microcrystalline collagen, based on said composition.

2. A composition according to claim 1, wherein the said pharmacologically active ophthalmic agent is selected from carbachol, a pilocarpine salt, an epinephrine salt, dexamethasone, phenylbutazone, sulphacetamide, hydrocortisone, chlorobutanol, prednisolone

acetate, phenylephrine hydrochloride, tropicamide, zinc sulphate, polymixin B sulphate, neomycin sulphate, atropine sulphate, triamcinolone acetonide and mixtures thereof.

3. A composition substantially as described in foregoing Formulation 1.

4. A composition substantially as described in foregoing Formulation 2.

5. A composition substantially as described in foregoing Formulation 3.

6. A composition substantially as described in foregoing Formulation 4.

7. A composition substantially as described in foregoing Formulation 5.

8. A composition substantially as described in foregoing Formulation 6.

9. A composition substantially as described in foregoing Formulation 7.

10. A composition substantially as described in foregoing Formulation 8.

11. A composition substantially as described in foregoing Formulation 9.

12. A composition substantially as described in foregoing Formulation 10.

13. A composition substantially as described in the foregoing Formulation 11.

14. A composition substantially as described in foregoing Formulation 12.

15. A composition substantially as described in foregoing Formulation 13.

16. A composition substantially as described in foregoing Formulation 14.

17. A composition substantially as described in foregoing Formulation 15.

18. A composition substantially as described in foregoing Formulation 16.

19. A composition substantially as described in foregoing Formulation 17.

20. A composition substantially as described in foregoing Formulation 18.

21. A composition substantially as described in foregoing Formulation 19.

22. A composition substantially as described in foregoing Formulation 20.

23. A composition substantially as described in foregoing Formulation 21.

24. A composition substantially as described in foregoing Formulation 22.

25. A composition substantially as described in foregoing Formulation 23.

26. A composition substantially as described in foregoing Formulation 24.

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